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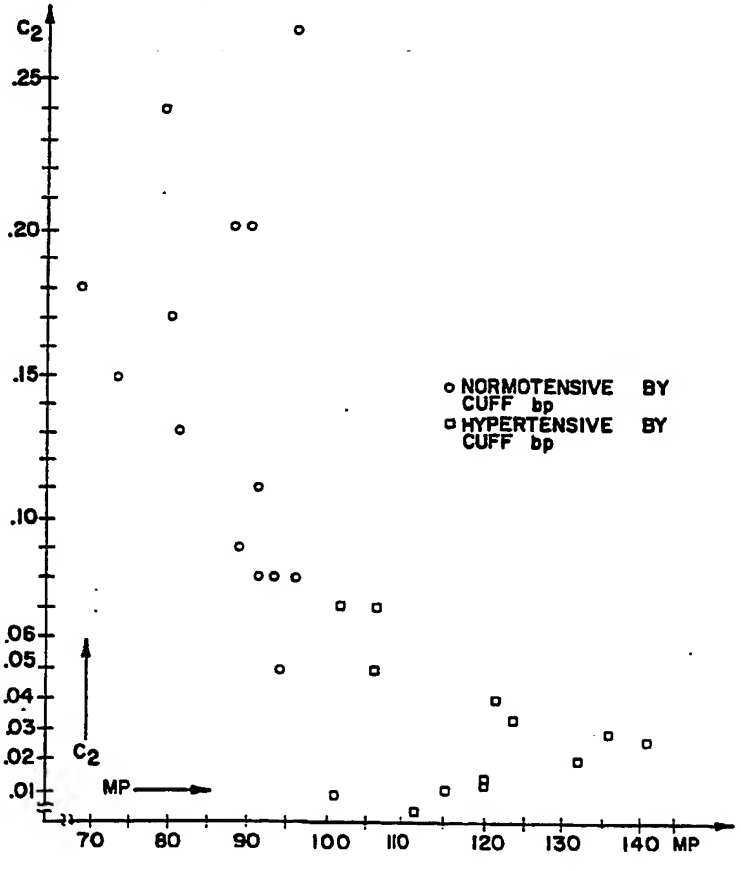
(54) Title: METHOD AND APPARATUS FOR DIAGNOSING, TREATING HYPERTENSION

(57) Abstract

A method for diagnosing, treating and monitoring hypertension uses the parameter C_2 (i.e. distal vascular compliance) of the modified Windkessel model as an indication of the hypertensive disease condition. Apparatus for determining the parameter C_2 of the modified Windkessel model includes means for obtaining a pressure pulse contour and a cardiac output value and for determining the model parameters.



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METHOD AND APPARATUS FOR DIAGNOSING, TREATING HYPERTENSION

This invention was made with Government support under Grant No. 5P01-HL 17871-07 and 1P01-HL 32427. The Government has certain rights in the invention.

Technical Field of the Invention

The present invention relates generally to the fields of cardiac and circulatory medicine, and more particularly to the medical disorder of hypertension.

Background of the Invention

Hypertension is traditionally defined as abnormally elevated blood pressure. More specifically, when a person under conditions of rest consistently has a blood pressure that exceeds 145/90 (systole/diastole), the person is said to have high blood pressure or hypertension. It is currently believed that over fifty million people in the United States have hypertension and fifteen to twenty percent of all deaths in people over fifty years of age occur as a direct or indirect result of hypertension. Actuarial statistics show that the disability and mortality rates of hypertensive persons are higher for each age bracket than for persons with normal blood pressure. Specific ailments attributable to hypertension include heart failure, myocardial infarction, rupture or thrombus of the blood vessels in the brain and kidney damage.

Despite the prevalence of hypertension and its potentially severe consequences to health, its detection, treatment and diagnosis remains entirely dependent on blood pressure measurements. However, the presence of high blood pressure in a patient at any given time only establishes that the patient's blood pressure at that moment is high; it says nothing about the patient's underlying medical condition. Substantial transient variations in blood pressure, for example as caused by ingestion, exercise, posture, circadian rhythms and emotional states, occur on a regular basis in any individual. Thus, it is not possible to tell, absent

continuous measurements and periodic followup over time, whether a hypertensive state is a function of a transient condition or is of a chronic nature. Blood pressure measurements in and of themselves do not reveal the presence of the hypertensive disease condition, which can be defined as the process or presence of underlying physical changes in the human body which result in the state of hypertension.

The inability to measure or detect the hypertensive disease condition as opposed to merely its ultimate effects, i.e. the state of elevated blood pressure, is a glaring and problematic deficiency in the diagnosis, treatment and care of hypertensive individuals. This deficiency manifests itself in various ways. For one, it can result in unnecessary and undesirable antihypertensive treatment for individuals who are diagnosed as borderline hypertensive due to an elevated blood pressure above the statistical norm of 145/90 but who are actually healthy and do not have the hypertensive disease condition. Administering antihypertensive therapy to such healthy patients would subject them to its potentially undesirable side effects. This is clearly ill advised. For another, certain individuals may exhibit normal blood pressure as it is statistically defined, yet suffer from the underlying hypertensive disease condition. These individuals may benefit from antihypertensive therapy yet it would not, according to current practices, be prescribed for them.

Without knowledge of underlying physical abnormalities, the severity or intractability of a particular case of hypertension cannot be determined without extended monitoring of the response of a patient to treatment. Furthermore, a predisposition to development of hypertension is impossible to ascertain other than by predictions made from the medical history of a patient's family. Thus, there is a strong need to

develop diagnostic tools for detecting and measuring the hypertensive disease condition.

A considerable amount of research has been conducted into the causes and effects of hypertension in humans. Most of this research has focused on the properties of the human vasculature which affect and control blood flow and blood pressure. For example, in the mid 1970's Thomas B. Watt, Jr. and Charles S. Burrus investigated the use of the modified Windkessel model to quantify properties of the human vascular system. The results of this investigation were published in their article entitled "Arterial Pressure Contour Analysis for Estimating Human Vascular Properties" Journal of Applied Physiology (1976) 40(2): 171-176. This article describes the experimental procedures and techniques used by Watt and Burrus to investigate the Windkessel model, and presents test data supporting their conclusions.

The modified Windkessel model investigated by Watt and Burrus is a third-order electrical model of the arterial system. The model includes two capacitive elements, C_1 and C_2, an inductance component L and a resistance component R. Hypothetically, C_1 corresponds to the "proximal vascular compliance", defined as the collective elastic compliance of major arteries nearest the heart, C_2 to that of "distal vascular compliance", defined as the vascular compliance of smaller peripheral arteries and arterioles further from the heart, L to the collective inertia of major blood columns, and R to the total vascular resistance assumed to be located primarily in arterioles and capillaries. These quantities all portray gross effective mechanical behavior of complex networks of blood-filled vessels.

As part of their investigation, Watt and Burrus determined the values for the model parameters for fifteen normal human subjects and for comparison four hypertensive patients. The fifteen normal subjects

studied were young adult males, mostly graduate students, who satisfied clinical criteria of cardiovascular normalcy. The data obtained showed that distal vascular compliance was distinctly lower in the hypertensive than in the normal subjects suggesting that the hypertensive patients had less compliant distal vessels than the normal subjects.

While the minimal data reported by Watt and Burrus suggested a connection between hypertension and reduced distal vascular compliance measurements (as quantified by the parameter C_2) the investigation was statistically inconclusive for want of data showing a continuum of blood pressure measurements and corresponding distal compliance measurements from which meaningful conclusions to the relationship between blood pressure and distal compliance could be drawn. In any event, the Watt and Burrus findings did not lead to further research on the relationship of distal vascular compliance to hypertension. In fact, as explained below, all of the known research conducted since the Watt and Burrus findings were published has focused on the relationship between proximal vascular compliance and hypertension. Thus, it is clear that the findings of Watt and Burrus did not suggest to one of ordinary skill in the art that distal vascular compliance could be an important and clinically useful marker or determination for the hypertensive disease condition. In fact, it would appear that just the opposite was true.

As noted above, despite the findings reported by Watt and Burrus in their 1976 paper, virtually all hypertension research conducted since that time to date has focused on studying the properties of the large, proximal arteries and the relationship of the properties of these arteries, in particular their vascular compliance, to hypertension. For example, the research group of Simon, Levenson and Safar et al. has conducted a

number of studies on the relationship between the vascular compliance of large arteries and hypertension. (See, for example, A. Simon, J. Levenson, J. Bouthier, and B. Maarek, "Haemodynamic Basis of Early Modifications of the Large Arteries in Borderline Hypertension:, (J-Hypertens., 1987 Apr. 5(2); P. 179-84); M.E. Safar and G.M. London, "Arterial and Venous Compliance in Sustained Essential Hypertension", (Hypertension, 1987 Aug. 10(2); P. 133-9); A.C. Simon, J.A. Levenson and M.E. Safar, "Hemodynamic Mechanisms of and Therapeutic Approach to Systolic Hypertension", (J-Cardiovasc. Pharmacol, 1985, 7 Suppl. 2; P S22-7); A.C. Simon, J.A. Levenson, A.M. Safar, J.D. Bouthier, and M.E. Safar, "ACE Inhibition and Brachial Artery Haemodynamics in Hypertension", (Er. J. Clin. Pharmacol. 1984, 18 Suppl. 2; P. 243S-247S); J. Levenson, A.C. Simon, J.D. Bouthier, A. Benetos and M.E. Safar, "Post-Synaptic Alpha-Blockade and Brachial Artery Compliance in Essential Hypertension", (J. Hypertens. 1984 Feb. 2(1); P. 37-41); D. Fitchett, J.D. Bouthier, A.C. Simon, J.A. Levenson, and M.E. Safar, "Forearm Arterial Compliance: The Validation of a Plethysmographic Technique for the Measurement of Arterial Compliance", (Clin. Sci. 1984 Jul. 67(1); P. 69-72); J.A. Levenson, A.C. Simon, M.E. Safar, J.N. Fiessinger, and E.M. Housset, "Systolic Hypertension in Arteriosclerosis Obliterans of the Lower Limbs", (Clin. Exp. Hypertens. [A] 1982, 4(7); P. 1059-72); A.C. Simon, M.E. Safar, J.A. Levenson, G.M. London, B.I. Levy and N.P. Chau, "An Evaluation of Large Arteries Compliance in Man", (Am. J. Physiol. 1979 Nov. 237(5); P. H550-4); and A.C. Simon, B.I. Levy, Y.A. Weiss, M.A. Kheder, J.M. Levenson and M.E. Safar, "Arterial Compliance in Permanent Essential Hypertension: Preliminary Report", (Angiology, 1987 May, 29(5); P. 402-9).

In many of the these studies, the Simon group characterized the compliance of the large arteries by use

of a first order resistance-capacitance (RC) electrical model. Using this model the Simon group found that the compliance of the large arteries was decreased in patients with essential hypertension. Similar results have been reported by others conducting similar research. A good representation of these findings is found, for instance, in the publication of Ventura et al., entitled, "Impaired Systemic Arterial Compliance in Borderline Hypertension", (Am. Heart J. 108: 132, 1984).

While both the Simon group and Ventura et al. reported that the compliance of the large arteries appeared to be reduced in hypertensive patients, the difference in the compliance of the large arteries of healthy and hypertensive patients is not great enough to make this compliance measurement clinically useful as a diagnostic tool for identifying patients with the hypertensive disease condition. The above-referenced publication of Ventura et al. shows several plots of compliance measurements for healthy vs. hypertensive groups. As can be seen from those plots, even though the average compliance measurement for healthy patients differs from that of hypertensive patients, many healthy, normotensive patients who did not have a hypertensive disease condition and would have had a normal distal compliance, had large-artery compliance measurements in the same range as those found for hypertensive patients. As a result, there is no distinct and clinically useful line dividing compliance measurements found in hypertensive patients from those found in normotensive patients. The compliance of large arteries is not a sensitive and discriminating enough of a marker for the hypertensive disease condition to be clinically useful.

Accordingly, despite years of research there is still a need for a clinically useful diagnostic tool for detecting and measuring the hypertensive disease

condition. As set forth below, the present invention finally provides such a tool.

Summary of the Invention

The present invention provides method and apparatus for the detection, diagnosis, monitoring and treatment of hypertension. More specifically, the present invention calls for measuring the distal compliance of a patient's vascular system and for using the measured compliance as a marker or indicator of the hypertensive disease condition. According to one aspect of the invention, the parameter C_2 of the modified Windkessel model is used as a measure of distal vascular compliance. According to another aspect of the invention, there is provided apparatus for monitoring blood pressure waves and determining the value of the parameter C_2.

Brief Description of the Drawings

Figure 1 is a skematic drawing of the modified Windkessel model of the human vasculature;

Figure 2 is a plot of mean arterial pressure (MAP) versus C_2 for a group of normotensive subjects and a group of hypertensive patients as diagnosed by blood pressure cuff (sphygmomanometer) measurements;

Figure 3 is a schematic block diagram of the monitor according to the present invention;

Figure 4a and 4b comprise a schematic flow chart of the software of the present invention;

Figure 5 is illustrative example of typical arterial pulse contours in healthy patients;

Figure 6 is illustrative example of typical arterial pulse contours in diseased patients;

Figure 7 is a schematic view diagram of the software to be used in the clinic computer according to the present invention;

Figure 8 is a plot of C_2 versus MAP for hyper- and normo-tensive patients; and

Figure 9 is a plot of C_1 versus MAP for hyper- and normo-tensive patients.

Detailed Description of the Invention

The present invention is based on the results of a study of the vasculature of a group of hypertensive patients and a group of normotensive patients. The hypertensive patients all had a confirmed history of elevated blood pressure with blood pressure cuff measurements exceeding 145/90 at the time of the study. The normotensive subjects all had blood pressure cuff measurements below 145/90. The modified Windkessel model of the arterial system is shown in Fig. 1. In the model, C_1 = proximal compliance (ml/mm Hg); C_2 = distal compliance (ml/mm Hg); L = inertence (mm Hg/ml/s(2)); P_1 = proximal arterial (aortic) pressure (mm Hg); P_2 = distal arterial (brachial) pressure (mm Hg); and R = peripheral resistance (dynes x seconds x cm^{-5}).

Blood pressure waveforms for each patient in the study were recorded from the brachial artery via an 18-gauge, 2 inch Teflon® catheter connected to a Statham P23Db pressure transducer. This catheter-transducer system has an undamped natural frequency higher than 25 Hz and a damping coefficient less than 0.5 as measured by balloon "pop" in the laboratory. This frequency response is adequate for the pulse-contour technique for obtaining measurements of the parameters of the modified Windkessel model. Aortic valve closure was determined from heart sounds obtained from the upper left sternal border. The beginning of the second heart sound (S_2) indicated the onset of diastole, and the upstroke of the brachial artery pulse was used to mark the end of diastole. A thermodilution balloon floatation catheter was positioned in the pulmonary artery after percutaneous insertion into

a brachial vein in the patient. Cardiac output was determined in triplicate by thermodilution. In normal subjects cardiac output was measured by the thoracic impedance using the Minnesota Impedance Cardiograph Model 30413.

Blood pressure waveforms were recorded for 30 seconds for each subject in a supine position, after at least 60 minutes of supine rest after catheter positioning. All hemodynamic data were recorded on both paper and magnetic tape. Data were digitized using a 12-bit analog to digital converter operating at 200 samples per second per channel. Digitized data were saved on disk for subsequent beat marking, signal processing and pulse-contour analysis. The onset and end of diastole for the brachial artery pressure waveform were marked on six consecutive beats and the modified Gauss-Newton parameter-estimating algorithm was run on each marked beat. Each group of six consecutive beats was selected manually from each 30-second record by choosing the group with the most noise-free pressure and phonocardiogram signals as viewed by the operator. The diastolic waveform for each beat can be represented most generally as the third-order function:

$$P(t) = A_1 e^{-A2t} + A_3 e^{-A4t} \cos(A_5 t + A_6)$$

The parameter-estimating algorithm calculated the optimal values for the Ai(i = 1....6) so that the estimated function fit the observed data with a minimum least square error. These Ai coefficients, mean pressure and cardiac output values were then used to determine the circuit elements (compliance, inertence and resistance) in the modified Windkessel model of the vasculature, in which the measure of brachial arteriole pressure was taken as $P_2(t)$. Heart rate, pulse velocity and wave reflections do not figure directly into determination of the circuit parameters. The results for each six consecutive beats were averaged and the mean values were

used in the statistical data analysis. Further details on the pulse-contour analysis of the study method are described below.

Fig. 2 shows the plotting of the mean arterial pressure (MAP) versus distal compliance as quantified by the measured C_2 parameter for all of the subjects in the study, with the normotensive patients represented by circles and the hypertensive patients represented by squares. For the sake of comparison, it is noted that mean arterial pressure is approximately equal to the diastolic pressure measurement plus one-third the difference between the systolic and diastolic measurements. For example, a 145/90 cuff measurement would equate to a mean arterial pressure of about 108 mm Hg.

As shown by the plot, C_2 varies widely in normotensive subjects but is consistently reduced in subjects with hypertension. The plot also shows a generally linear decrease in the measured C_2 compliance value with increase in mean arterial pressure. The results of this study thus establish: 1) hypertensive subjects have consistently reduced distal vascular compliance; 2) distal vascular compliance is independent of blood pressure, i.e. two persons with the same blood pressure can have widely varying distal compliance, particularly among normotensive subjects; 3) there is a distinct division between distal vascular compliance measurements for normotensive and hypertensive patients; and 4) the underlying physical condition of distal vascular compliance, as quantified by C_2 measurements, can be used as a marker for or an indicator of the hypertensive disease condition. The study also supports the following inferences: 1) a normotensive or borderline hypertensive patient with a normal C_2 value is unlikely to develop the hypertensive disease condition and its associated chronic hypertension; and 2) normotensive or

borderline hypertensive subjects with reduced C_2 values are more likely to develop chronic hypertension than normotensive or borderline hypertensive subjects with normal C_2 values.

The results of the study described and discussed above thus establish that distal vascular compliance is a specific marker for the hypertensive disease condition and that diagnosis and drug therapy of the disease called hypertension can be made more precise by measurement of C_2 than by measurement of cuff blood pressure alone. As noted above, the blood pressure may vary widely and may be normal on many occasions in some patients who have the hypertensive disease condition and may be high on occasions in patients who do not have the hypertensive disease condition. Thus, the measurement of blood pressure alone is not useful in identifying patients who have the hypertensive disease condition. However, the C_2 measurement will be reduced in patients who have the hypertensive disease condition regardless of blood pressure and will be normal in patients who do not have the hypertensive disease condition regardless of their blood pressure. Therefore, distal vascular compliance (i.e. C_2 measurements) can serve the unique purpose of identifying the hypertensive disease condition, particularly in patients with borderline blood pressures which may sometimes be normal and sometimes be elevated.

The use of distal vascular compliance as a marker for the hypertensive disease condition has several important clinical applications, some of which are specified as follows. For one, distal vascular compliance measurements can be used to exclude from unnecessary antihypertensive therapy, patients whose blood pressure may periodically be elevated but who do not actually have the hypertensive disease condition. To this end the present invention provides a method for determining treatment for a patient with borderline

hypertension comprising: 1) determining for the patient a measure of distal vascular compliance; and 2) administering medications known to raise distal vascular compliance (i.e. make the vessels less stiff and more elastic) if said distal compliance is less than the threshold band defined below. Alternatively, or in addition, the patient can be identified as one not likely to benefit from administration of medication which increases distal compliance if the patient's distal compliance is greater than the threshold band defined below. According to this method, a patient is defined as borderline hypertensive if his blood pressure is sometimes elevated and in the hypertensive range but is at other times is normotensive. By use of this method, many patients can be spared from the potentially serious side effects and inconvenience of antihypertensive drug therapy, and, moreover, the cost of their medical care can be reduced.

Another application of the present invention is the use of distal vascular compliance measurements for identifying the hypertensive disease condition and/or quantifying its severity. This method comprises the steps of: 1) determining for the patient a measure of distal vascular compliance; 2) diagnosing the patient as having the hypertensive disease condition if his distal vascular compliance is within or less than a predetermined diagnostic threshold band; and 3) diagnosing the patient as not having the hypertensive disease condition if his distal compliance is greater than the threshold band. The threshold band is the summed region of individual vascular compliance values taken from a statistically significant number of patients who have been diagnosed as having mild to severe hypertension.

In the alternative, an average threshold value can be obtained by averaging the hypertensive patient

compliance values that establish the foregoing threshold band. This threshold value can be substituted for the threshold band in the foregoing method. Patients with a distal vascular compliance less than or about equal to this average threshold value are diagnosed as having the hypertensive disease condition (such patients may have normal or elevated blood pressure). Patients with a distal vascular compliance greater than the average threshold value are diagnosed as being essentially free of the hypertensive disease condition. A conservative approach can also be employed whereby only those patients having a distal compliance greater than the average threshold value plus its standard deviation are diagnosed being essentially free of the hypertensive disease condition.

According to another embodiment of this method, persons determined to be hypertensive by blood pressure cuff measurements can be further tested to determine their distal vascular compliance. If their distal vascular compliance is above a certain level, the person can be diagnosed as not likely to benefit from antihypertensive drug therapy designed to raise distal vascular compliance and, moreover, as perhaps only suffering from a transient elevation of blood pressure.

According to another embodiment of this method, the distal vascular compliance measures can be used to assess the severity and/or the likelihood that a particular individual with hypertension will respond to treatment. For instance, persons with only marginally high blood pressure but having very poor distal compliance, e.g. C_2 measurements of about 0.02 ml/mm Hg, can be classified as having a severe hypertensive disease condition (although they are only mildly hypertensive).

This diagnosis would indicate that the patient requires extensive therapy and followup. Moreover, such

a patient may greatly benefit from antihypertensive drug therapy to raise their distal vascular compliance.

According to yet another application of the discovery of the present invention, there is provided a method for early detection of the development of the hypertensive disease condition comprising the steps of: 1) measuring the distal vascular compliance of the patient; 2) repeating step 1) over a period of time and charting the course of distal vascular compliance; and 3) diagnosing a movement toward the onset of the hypertensive disease condition if the course of charted distal compliance is trending downwardly indicating stiffening or hardening of distal arteries.

Another application of the discovery of the present invention comprises a method for monitoring the progress of the hypertensive disease condition comprising the steps of:

1) measuring the distal vascular compliance of the patient; 2) repeating step 1) over a period of time and charting the course of distal vascular compliance; and 3) diagnosing the progress of the hypertensive disease condition based on said charted course, said progress being diagnosed as unchanged if said measures stay substantially unchanged over time, worsening if said measures decrease over time indicating decreasing distal compliance, and improving if said measures increase over time indicating increasing distal compliance.

The foregoing applications of the present invention employ distal compliance as a marker of or indicator for the hypertensive disease condition. These applications provide methods for detecting, diagnosing, monitoring and treating the hypertensive disease condition. In the specific methods outlined above the present invention contemplates using the C_2 parameter of the modified Windkessel model as a measure of distal vascular compliance. It shall be understood, however, that other

measures of distal compliance, if developed, would also work in applying the various methods and principles of the present invention contemplated herein. Moreover, it shall be understood that "distal vascular compliance" as that term is used herein is in essence defined as the physiologic attribute measured by the C_2 and is influenced by other processes in the vascular system including cardiovascular aging; atherosclerosis; medial arteriosclerosis; vascular infiltrative processes; vascular inflammatory processes; vascular hypertrophy and other deleterious vascular conditions which are not presently ellucidated, and which would produce a reduction of C_2 values. Accordingly, it shall be understood that the use of other measurement methods for determining vascular compliance and identifying underlying disease states such as those mentioned in the foregoing discussion, are within the scope of the methods and principles of the present invention.

According to the results of the study disclosed herein, a distal vascular compliance within or below a C_2 threshold band of from about 0.05 to 0.08 indicates, with a reasonably high degree of certainty, that the patient has a vascular abnormality or abnormalities associated with hypertension, aging, atherosclerosis or other vascular disease. Under the alternative average threshold value method, a distal vascular compliance at or below a C_2 threshold value of about 0.05 ml/mm Hg indicates, with a high degree of certainty, that the patient is suffering from the hypertensive disease condition and/or another vascular abnormality(ies).

The particular C_2 value selected as the threshold value for individual clinical application is to some degree a matter of choice. For instance, it may be desirable to diagnose borderline hypertensive patients (i.e. those diagnosed through repeated blood pressure measurements) with C_2 measurements below a threshold value

of about 0.12 ml/mm Hg as likely to benefit from antihypertensive therapy directed toward raising distal vascular compliance. In such cases antihypertensive therapy might reduce the patient's prevailing blood pressure level so that transient increases in blood pressure, as for example caused by stress, would not exceed dangerous levels whereby a blood vessel might rupture and result in a stroke.

As contemplated by the conservative diagnostic approach described above, when employing the average threshold value method, it may be desirable to choose a second, different average threshold value above which the patient is diagnosed as being essentially free from a hypertensive disease condition. For instance, the results presented herein indicate that a patient with a distal vascular compliance at or above an average threshold C_2 value of about 0.08 ml/mm Hg would, with a high degree of certainty, be essentially free of the hypertensive disease condition. Patients with C_2 values between those of the average hypertensive and normotensive threshold values, i.e. those within the threshold range, could be diagnosed as borderline cases if other clinical conditions are confirmatory.

The present invention also provides apparatus for measuring, monitoring and diagnosing the hypertensive disease condition. The vascular compliance apparatus 10 according to the present invention is shown in schematic block diagram form in Fig. 3. The monitor 10 includes an analog to digital convertor (A/D) 12, preferably 12-bit, a microprocessor unit 14, for instance a 6502 model by Synertek, a keyboard input 16, display 18, ROM 20, RAM 22 and modem 24. An input port 30 is provided to receive analog signal input from an arterial pressure transducer 34. A printer output port 38 and a telephone port 40 are provided from microprocessor 14 and modem 24, respectively.

Transducer 34 is preferably a Statham P23Db pressure transducer, and it is preferably connected to a brachial artery by an 18-gauge, 2-inch Teflon catheter. This catheter-transducer system has an undamped natural frequency higher than 25 HZ and a damping coefficient less than 0.5, providing an acceptable frequency response. It shall be understood, however, that while the brachial artery is preferred, other arterial peripheral locations for obtaining the pulse pressure contour could readily be substituted. Moreover, it is contemplated that a non-invasive method for measuring arterial pressure waves could also be used.

The software component 50 of the monitor 10 is illustrated in block diagram flow-chart form in Figs. 4a and b. Software within 10 is preferably maintained in ROM 20 and is referenced by microprocessor 14. Alternatively, software 50 could be stored in magnetic form on a floppy computer disk connected so as to be accessed by monitor 10. Generally, speaking, software 50 runs on microprocessor 14 to control the acquisition of artery pressure pulse data, and to process, analyze and diagnose the acquired data.

An initialization and mode select routine 52 is provided for initializing microprocessor 14, including prompting the user to enter the date (and certain desired patient information). Routine 52 further allows either the monitor mode or communication mode to be selected. If the monitor mode is selected, A/D convertor 12 is activated (54) to digitize the analog brachial pressure pulse signal generated by transducer 34 in its position in the patient's brachial artery. Referring to Figs. 5 and 6, there are illustrated typical brachial artery pulse pressure contours for healthy, normotensive and hypertensive patients, respectively.

The present invention uses an A/D sampling rate of 200 samples/second, which is satisfactory to capture the

highest frequency components of interest in the brachial pressure pulse. It shall be understood, however, that higher or lower sampling rates may be used, and that the invention is in no way limited to the 200 samples/second rate. Routine 56 provides that the artery is monitored for approximately 30 seconds, producing in the range of 25 to 60 digitized pulses, depending on the heart rate. The stream of digitized pulses are stored in RAM 22 in the form of a continuous series of periodic time dependent data byte samples, with each data byte corresponding to the instantaneous pressure of the artery.

Routine 60 is provided for acquiring a cardiac output value, which is required for calculation of impedance parameters as explained in more detail below. In the present embodiment cardiac output is input directly from keyboard 16 in liters/minute (or alternatively, milliliter/second). Cardiac output may be determined by the thoracic impedance technique using for example the Minnesota Impedance Cardiograph model 30413, with the results being manually transferred to apparatus 10. Alternatively, it is contemplated that another non-invasive instrument may be used for this purpose, with the measured output being transmitted directly into monitor 10 through a microprocessor port. There are, of course, well-known invasive techniques for determining cardiac output.

A selection routine 20 is also provided to analyze the recorded waves and to select a group of at least six consecutive representative beats preferably of comparatively low noise content. Representative beats are identified by establishing windows of permissible heart rate and mean arterial pressure values whereby abnormally fast or slow heartbeats, or high or low pressures can be rejected. The routine can thus pick the series of beats which is most representative. Where

possible it is preferable that the windows be tailored to the patient, thus allowing more precise selection of representative beats.

Because only the diastolic portion of each selected beat is of interest, i.e. that part of the pressure wave which corresponds to the period of diastole in the heart, a routine 72 is provided to identify the relevant portions. When marked manually, a clinician can identify the onset of diastole by correlating to the second heart sound S_2, and the end of diastole by the upstroke of the following pulse. For example, in Figs. 5 and 6 diastole is marked by the respective segments A and B. However, for the sake of simplicity the present invention uses a software analysis algorithm to predict and select the segment in each wave most probably corresponding to diastole. It is, however, important that the onset of the wave to be used occurs after the peak in the systolic wave and preferably twenty to fifty milliseconds before the dicrotic notch. Thus, routine 72 searches for the dicrotic notch (D), and marks the onset of diastole just before the location of the dicrotic notch on the wave. The end of diastole in the waveform is easily located by finding the upstroke of the next pulse. Alternatively, device 10 could include means for digitizing an analog signal representing the heart sounds, and software for identifying the second heart sound S_2 and correlating it to the digitized arterial waveform to identify the onset of diastole. This process could also preferrably be accomplished by a computer software program. With the relevant segments marked the data for each pulse can be analyzed to reveal the vascular compliance properties of the patient.

As referred to above, the modified Windkessel model of the arterial system is used in the pulse contour analysis of the present invention. As described above,

the model includes components P_1, P_2, C_1, C_2, L and R in which:

C_1 = proximal vascular compliance (ml/mm Hg)

C_2 = distal vascular compliance (ml/mm Hg)

L = inertance (mm Hg/ml/s^2)

P_1 = proximal arterial pressure (mm Hg)

P_2 = brachial artery pressure (mm Hg)

R = peripheral resistance (dynes x seconds x cm^{-5})

As taught for example by Goldwyn and Watt in I.E.E.E. Trans. Biomed. Eng. 1967; 14:11:-17, the disclosure of which is incorporated by reference herein, P_2 of the modified Windkessel model may be represented by the third order equation:

$P_2(t) = A_1\exp(-A_2t)+A_3\exp(-A_4t)\cos(A_5t+A_6)$, wherein:

$$C_1 = \frac{mp-p}{mp}\quad\frac{1}{R}$$

$$C_2 = \frac{1}{M}\quad\frac{1}{R}$$

$$L = \frac{m^2}{mn-p}\ R \text{ and}$$

wherein:

$$m = A_3 + 2\ A_5$$

$$n = 2\ A_3\ A_5 + A_5^2 + A_6^2$$

and

$$p = A_3(A_5^2 + A_6^2)$$

Thus, knowing R, which can be calculated from cardiac output and mean arterial pressure as follows:

$$R = \frac{\text{mean arterial pressure}}{\text{cardiac output}},$$

C_1, C_2, and L are readily calculated.

To accomplish the above, software 50 includes routine 80-82, which comprises a modified Gauss-Newton parameter-estimating algorithm as for example referenced by Watt and Burrus in their paper entitled "Arterial Pressure Contour Analysis for Estimating Human Vascular

Properties", Journal of Applied Physiology, 1976; 40:171-176, the disclosure of which is hereby incorporated herein by reference. Routine 80-82 calculates the optimal values for coefficients A_1-A_6, using the measured brachial arterial pressure as $P_2(t)$. The algorithm uses an iterative approach which preferably provides fast convergence. The algorithm used in routine 80-82 includes certain modifications. An automatic stopping procedure is included to stop iteration when an acceptable error level in the curve fitting threshold is reached or when convergence provides no further substantial fit of the curve. Also, when the process begins to diverge, it returns to the previous best case. The routine also includes a weighted iteration interval to improve convergence.

Once the coefficients A_1-A_6 are established for each pulse contour, the coefficients are used at routine 84 to calculate the C_1, C_2 and L vascular impedance parameters for each pulse contour. C_1, C_2 and L are all calculated in accordance with the formulas given above. Once calculated for each pulse contour the calculated values are average at routine 86, producing mean values more reliable for accuracy than any individual values. It shall be understood, however, that the averaging process is not essential. For instance, a median value could be selected for use if desired. After calculation, the distal compliance parameter C_2 is stored in RAM 22. Monitor 10 is further operative to analyze the acquired distal vascular compliance values in order to indicate the likelihood of unlikelihood of the hypertensive disease condition in the patient being monitored. In the present embodiment, diagnostic analyses are performed at the end of each monitoring operation. It is contemplated, however, that diagnosis could be initiated under independent keyboard 16 control if desired. The first diagnostic test performed is preferably a threshold

test, performed at routine 100 to determine whether the distal compliance (C_2) value is above, below or in between one or more threshold values which are preferably predetermined and stored in RAM 22 and RAM 20. Routine 100 can be programmed in accordance with the diagnostic methods outlined hereinabove.

Optionally, routines 102 and 110 are also provided for diagnostic purposes, and provide for analyzing distal vascular compliance values accumulated over time to determine the slope or trend of the values over time, for instance over a month or a year. Thus, routines 102 and 110 can anticipate a trend toward the hypertensive disease condition as indicated by diminishing distal vascular compliance values and evaluate the significance or abruptness of the trend. Conversely, a trend toward improved distal compliance can also be determined, indicating an improvement of the hypertensive disease condition, as may result from beneficial therapy. Routine 110 also optionally includes diagnostic logic to evaluate the interrelationship between C_2 values and the slope of the values, or other desirable criteria, to provide more sophisticated diagnosis.

Routine 120 is provided to indicate via display 18 the value of the C_2 parameter determined by the software, and the result of the threshold tests provided at routine 100, whereby, for instance, when distal compliance falls below the selected threshold value, a likelihood of the hypertension disease condition is indicated. Routine 140 is also provided to report (140) the analysis results on an optional printer 42.

In case the diagnosis indicates a potentially serious hypertension disease condition as may be indicated by an extremely low C_2 value or a trend as may be indicated for example by a severe downward distal compliance slope a warning routine 130 is provided to cause monitor 10 to produce a warning indication, either

through display 18, or in a printed report (140) the analysis results on an optional printer 42.

Monitor 10 also includes communications capability, whereby accumulated C_2 data (or, if desired other stored vascular parameters) may be communicated to further computer equipment 44 in a clinic or hospital, such as a personal computer or minicomputer. Accordingly, monitor 10 may be used by a patient at home with measured and stored parameters particularly C_2, being transmitted back to a treating hospital or clinic for review or for further analysis. For this purpose software 50 provides a communications mode including routines 145 and 146, which provide for establishing a communication link with remote system and for downloading selected information including accumulated C_2 values.

As shown in Figure 1, a clinic or hospital computer 44 is provided to communicate with monitor 10 using a standard modem-telephone link. Figure 7 illustrates in diagrammatic form the software 150 provided for clinic computer 44. A routine 152 is provided for establishing the communication link with monitor 10. Computer 44 preferably includes an auto-answer modem so that monitor 10 may establish unication therewith with a minimum of effort. Data acquisition routine 154 is provided to receive C_2 values and other desired data which may be stored in RAM 22, such as cardiac output, mean arterial pressure, C_1, L and slope data.

Routine 156 is provided to evaluate C_2 and, optionally, other vascular properties. Routine 156 includes all the capabilities described with respect to monitor 10 (routines 100, 102, 110), and preferably more sophisticated analysis techniques which would take into account other known patient data, such as the patient's medical history. At a minimum, routine 156 provides for a printed report of acquired C_2 values which may be reviewed by the treating personnel or physician.

Finally, a routine 158 is provided to suggest therapy strategy based on the results of evaluation 156.

The following example further illustrates the invention described above. The example, however, is not meant to constitute a limitation of the foregoing description. Variations of the method employed as characterized by the foregoing discussion are possible and useful also.

Example

The study described in the foregoing section was extended to include a larger group of hypertensive (hyp) and normotensive (N) Patients. The MAP (mean arterial blood pressure), C_1 and C_2 were determined for these patients as described above. The protocol employed was as follows.

Fifty-eight subjects ranging in age from 19 to 71 years (mean age 44 years) were recruited from the Minneapolis, Minnesota hospitals and medical schools. Each patient gave informed consent prior to the study. Patients were excluded if they manifested signs or symptoms of cardiac, renal, or pulmonary disease by undergoing an extensive history and physical exam. Laboratory analysis of each patient was also performed, including serum chemistries, electrolytes, ECG, and chest X-ray. If patients were being treated for hypertension pharmacologically, they were instructed to discontinue medications at least two weeks prior to their study date. Patients were also instructed to refrain from consuming food, alcohol, or caffeinated beverages, and from smoking tobacco, at least 8 hours prior to study.

Each patient was catheterized with an 18 gauge transcutaneous Teflon catheter inserted into his brachial artery. Pressures were obtained from a Statham P23b pressure transducer connected to the catheter. The procedures for inserting the catheter, measuring and

recording waveform cardiac output and computing values for C_1 and C_2 were applied as described in the foregoing section.

The results of the MAP, C_1 and C_2 measurements and the hyper-(hyp) or normo-(N) tensive nature of each patient (identified by ID number) are summarized in Table 1. The average C_2 hyp measurement is 0.018 with a deviation of 0.025. The average C_2 N measurement is 0.115 with a deviation of 0.06.

Table 1

Distal and Proximal Vascular Compliance

ID	MAP	C1	C2	DX	ID	MAP	C1	C2	DX	ID	MAP	C1	C2	DX
1	124	2.23	0.033	hyp	20	81	2.14	0.133	N	39	70	4.08	0.145	N
2	141	1.78	0.026	hyp	21	79	1.59	0.24	N	40	88	2.21	0.119	N
3	120	1.6	0.012	hyp	22	90	1.98	0.195	N	41	97	1.34	0.029	N
4	101	1.48	0.01	hyp	23	67	1.58	0.179	N	42	68	2.33	0.088	N
5	120	1.44	0.016	hyp	24	73	2.67	0.15	N	43	71	1.54	0.114	N
6	111	1.42	0.006	hyp	25	94	1.15	0.051	N	44	97	1.48	0.042	N
7	115	1.21	0.011	hyp	26	96	1.72	0.075	N	45	94	1.91	0.096	N
8	102	2.6	0.074	hyp	27	85	3.12	0.083	N	46	108	1.32	0.022	hyp
9	122	1.2	0.044	hyp	28	71	3.07	0.202	N	47	133	0.64	0.002	hyp
10	132	1.2	0.017	hyp	29	75	1.84	0.089	N	48	137	1.26	0.006	hyp
11	106	1.1	0.047	hyp	30	103	1.24	0.043	N	49	122	1.36	0.029	hyp
12	136	0.37	0.026	hyp	31	81	1.44	0.148	N	50	135	0.7	0.003	hyp
13	80	2.5	0.168	N	32	80	1.5	0.065	N	51	117	0.99	0.014	hyp
14	88	2.82	0.196	N	33	79	1.42	0.041	N	52	108	1.21	0.017	hyp
15	91	1.67	0.08	N	34	84	2.31	0.059	N	53	112	1.32	0.002	hyp
16	89	1.82	0.087	N	35	79	2.5	0.079	N	54	117	1.35	0.017	hyp
17	96	2.16	0.265	N	36	78	1.5	0.056	N	55	116	0.96	0.004	hyp
18	91	2.56	0.112	N	37	98	2.42	0.155	N	56	144	0.89	0.001	hyp
19	39	1.52	0.077	N	38	72	2.39	0.127	N	57	109	1.31	0.005	hyp
										58	121	0.83	0.002	hyp

The C_2 results from this study are plotted against MAP in Figure 8. The "O" points are hypertensive. The "X" points are normotensive. The plot shows that C_2 values of hypertensives consistently fall at or below 0.05 ml/mmHg and define a readily discernable threshold band in the hypertensive MAP region. This band recognizably falls below the normotensive C_2 region.

The C_1 results from this study are plotted against MAP in Figure 9. The "O" and "X" points have the same representations as in Figure 8. Here, however, the spread of C_1 values among the hypertensive patients is great and the band defined by this spread greatly overlaps the normotensive region. The plot shows that C_1 would provide a number of false positives and negatives if employed to indicate the presence of a hypertensive disease condition.

Although the invention has been described here in its preferred form, those skilled in the art will readily recognize that many modifications and changes may be made thereto without departing from the spirit and scope of the claims appended hereto.

I CLAIM:

1. A method for diagnosing the hypertensive disease condition in a human patient comprising the steps of:

a) measuring the distal compliance of the patient's vasculature; and

b) diagnosing the patient as having a hypertensive disease condition if his measured distal vascular compliance is within or below a threshold band of predetermined distal vascular compliance measurements.

2. A method for treating a patient with borderline hypertension as indicated by his blood pressure comprising the steps of:

a) measuring the distal compliance of the patient's vasculature; and

b) administering medications known to raise said measured distal vascular compliance value if the patent's measured distal compliance is below a predetermined threshold value.

3. A method for diagnosing a hypertensive disease condition in a patient comprising the steps of:

a) measuring the distal compliance of the patient's vasculature; and

b) diagnosing the patient as having the hypertensive disease condition for said patient if the patient's measured distal vascular compliance is at or below a predetermined threshold value.

4. A method for diagnosing a hypertensive disease condition in a patient comprising the steps of:

a) measuring the distal compliance of the patient's vasculature;

b) diagnosing the patient as having a hypertensive disease condition if his distal vascular compliance is at or below a first predetermined threshold value;

c) diagnosing the patient as not having a hypertensive disease condition if his distal vascular compliance is at or above a second predetermined threshold value; and

d) diagnosing the patient as having a hypertensive disease condition if his distal vascular compliance falls between the first and second threshold values and he has other indications of hypertension.

5. A method for early detection of the onset of the hypertensive disease condition in a patient comprising the steps of:

a) measuring repeatedly over a period of time the distal compliance of the patient's vasculature; and

b) diagnosing a movement toward the onset of the hypertensive disease condition if the repeated measurements of distal compliance have a downward trend in value.

6. A method for monitoring the progress of the hypertensive disease condition comprising the steps of:

a) measuring repeatedly over a period of time the distal compliance of the patient's vasculature; and

b) diagnosing the progress of the hypertensive disease condition based on the trend of the distal vascular compliance measurements as a function of time, said progress being diagnosed as unchanged if said distal vascular compliance stays substantially unchanged over time, worsening if said distal compliance decreases over time, and improving if said distal compliance increase over time.

7. A method according to any of claims 1 through 6 wherein said measure of distal vascular compliance is the parameter C_2 of the modified Windkessel model.

8. A method according to claim 1 wherein the measure of distal vascular compliance is the parameter C_2 of the modified Windkessel model and the threshold band is a Windkessel C_2 band from about 0.05 to about 0.08 ml/mmHg.

9. A method according to claim 2 wherein the measure of distal vascular compliance is the parameter C_2 of the modified Windkessel model and the threshold value is about 0.05 ml/mmHg.

10. A method according to claim 3 wherein said measure of distal vascular compliance is the parameter C_2 of the modified Windkessel model and said threshold value is about 0.05 ml/mmHg.

11. A method according to claim 4 wherein said measure of said distal vascular compliance is the parameter C_2 of the modified Windkessel model, the first predetermined threshold value is about 0.05 ml/mmHg, and the second predetermined threshold value is about 0.08 ml/mmHg.

12. A method according to any of claims 1 through 6 and 8 through 10 wherein the hypertensive disease condition is the result of reduced vascular elasticity, cardiovascular aging, arterosclerosis, vascular infection, vascular hardening, the formation of deposits on the vascular walls or combinations thereof.

FIG. 1

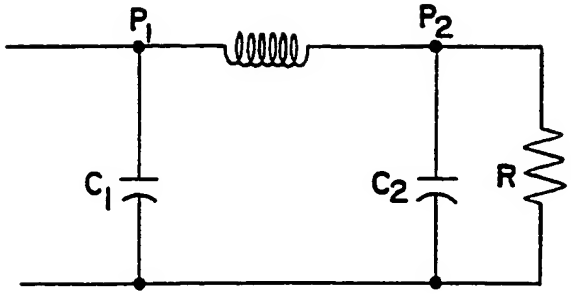
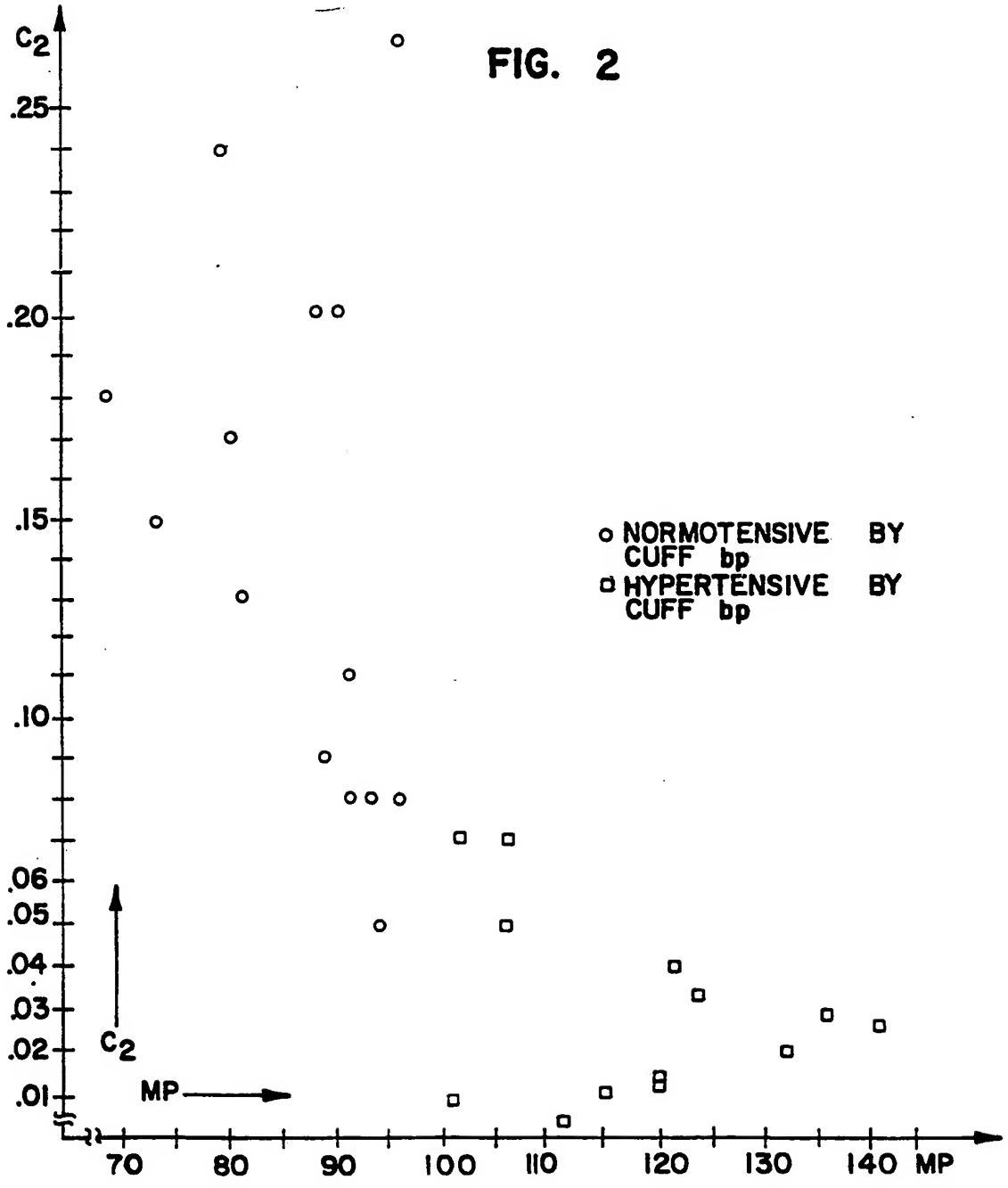

P1
P2
C1
C2
R

FIG. 2


C2
.25
.20
.15
.10
.06
.05
.04
.03
.02
.01
C2
MP
70
80
90
100
110
120
130
140
MP
o NORMOTENSIVE BY CUFF bp
□ HYPERTENSIVE BY CUFF bp

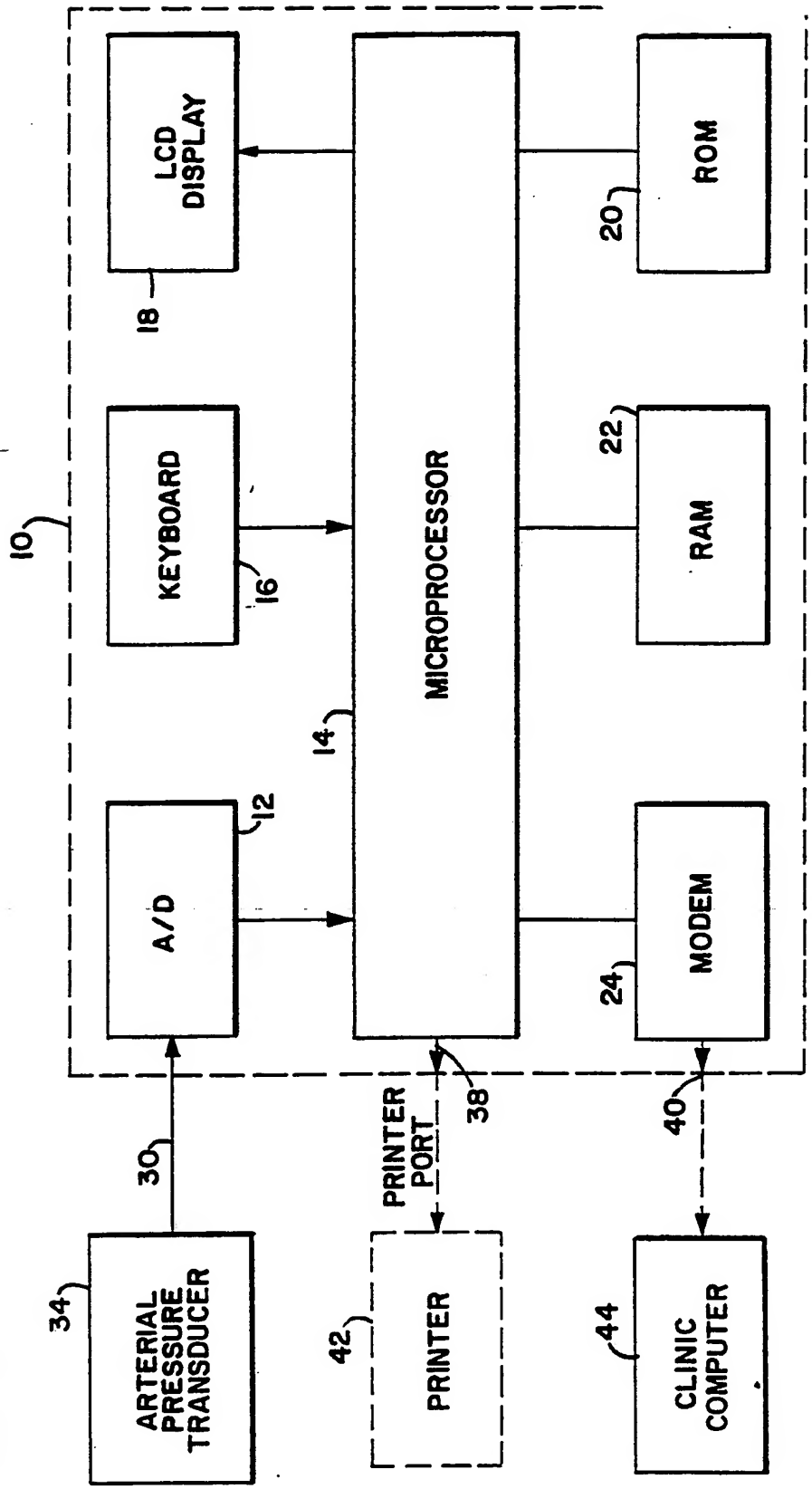

LCD DISPLAY
18
ROM
20
KEYBOARD
16
MICROPROCESSOR
14
RAM
22
10
A/D
12
MODEM
24
30
PRINTER PORT
38
40
ARTERIAL PRESSURE TRANSDUCER
34
PRINTER
42
CLINIC COMPUTER
44

FIG. 3

FIG. 4A

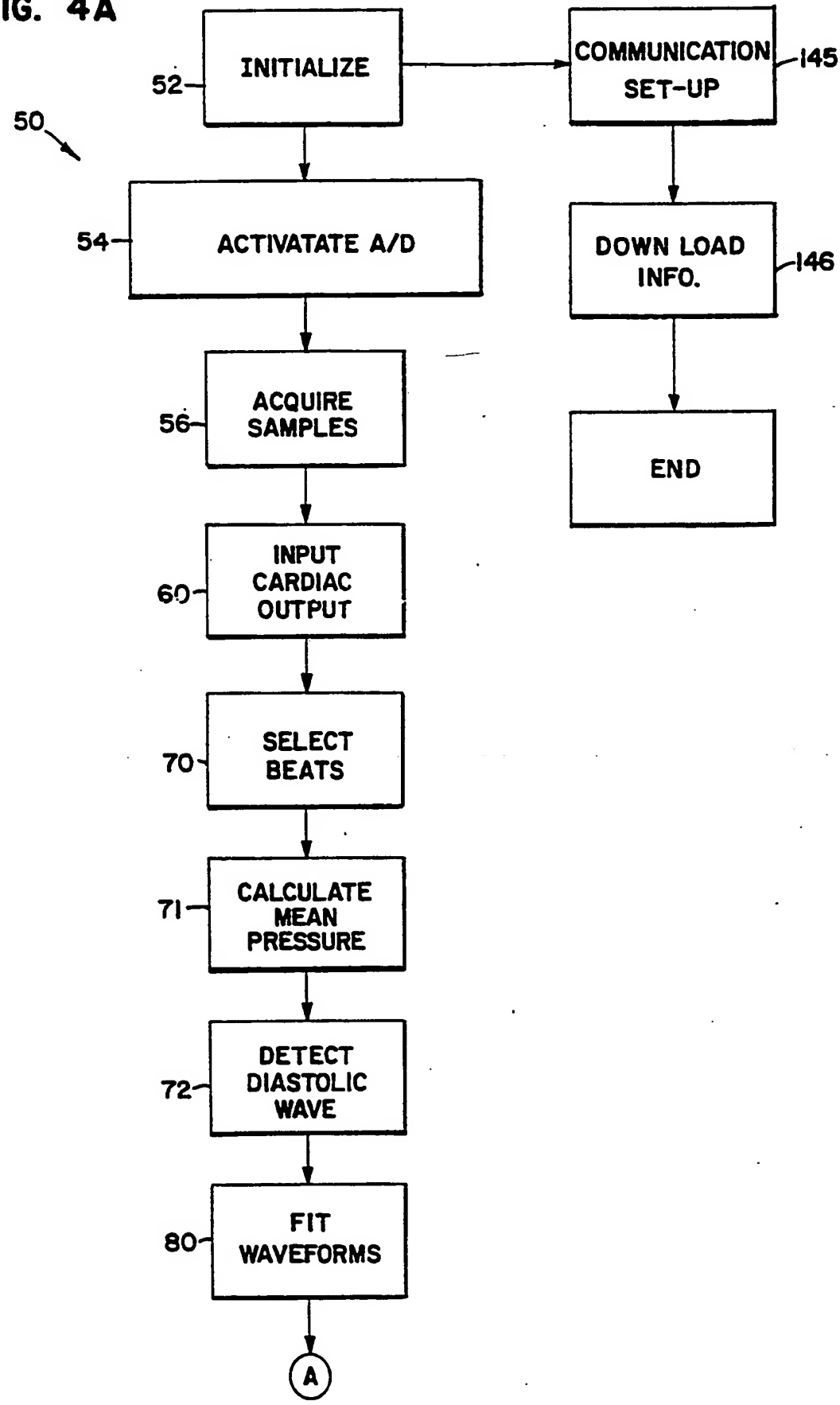
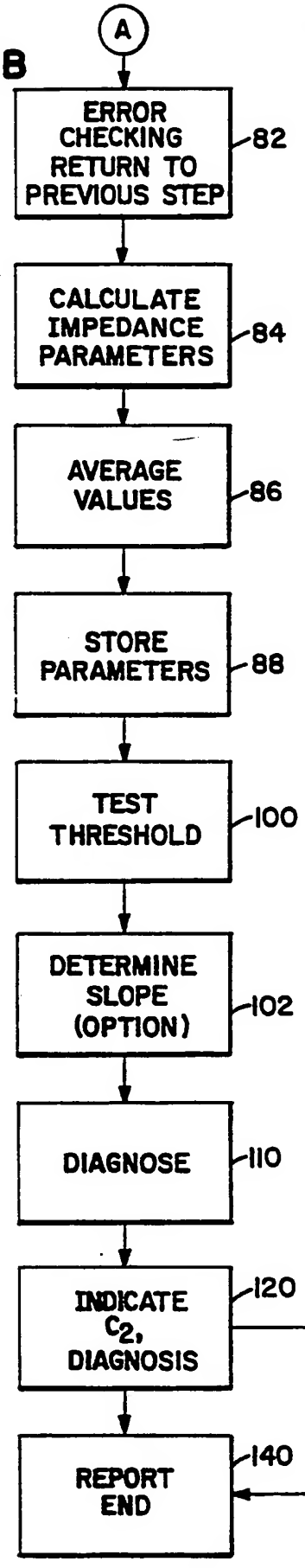

50
52
INITIALIZE
COMMUNICATION SET-UP
145
54
ACTIVATATE A/D
DOWN LOAD INFO.
146
56
ACQUIRE SAMPLES
END
60
INPUT CARDIAC OUTPUT
70
SELECT BEATS
71
CALCULATE MEAN PRESSURE
72
DETECT DIASTOLIC WAVE
80
FIT WAVEFORMS
A

FIG. 4B


A
ERROR CHECKING RETURN TO PREVIOUS STEP
82
CALCULATE IMPEDANCE PARAMETERS
84
AVERAGE VALUES
86
STORE PARAMETERS
88
TEST THRESHOLD
100
DETERMINE SLOPE (OPTION)
102
DIAGNOSE
110
INDICATE C_2, DIAGNOSIS
120
130
WARNING
REPORT END
140

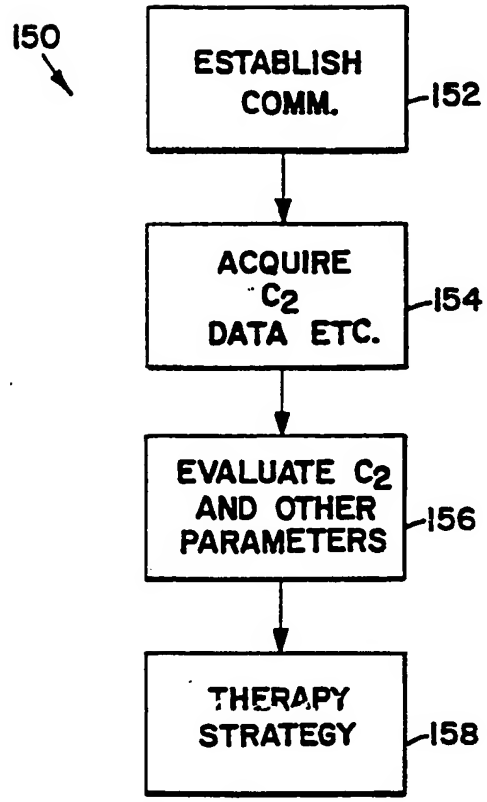

150
ESTABLISH COMM.
152
ACQUIRE C_2 DATA ETC.
154
EVALUATE C_2 AND OTHER PARAMETERS
156
THERAPY STRATEGY
158

FIG. 7

FIG. 5

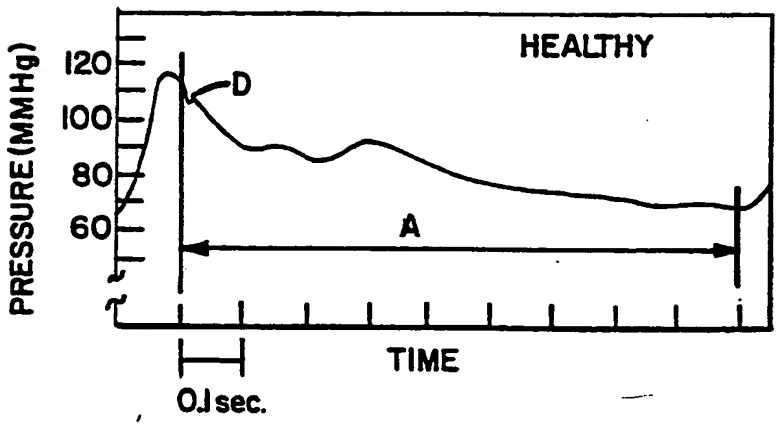

HEALTHY
120
100
80
60
PRESSURE (MM Hg)
D
A
TIME
0.1 sec.

FIG. 6

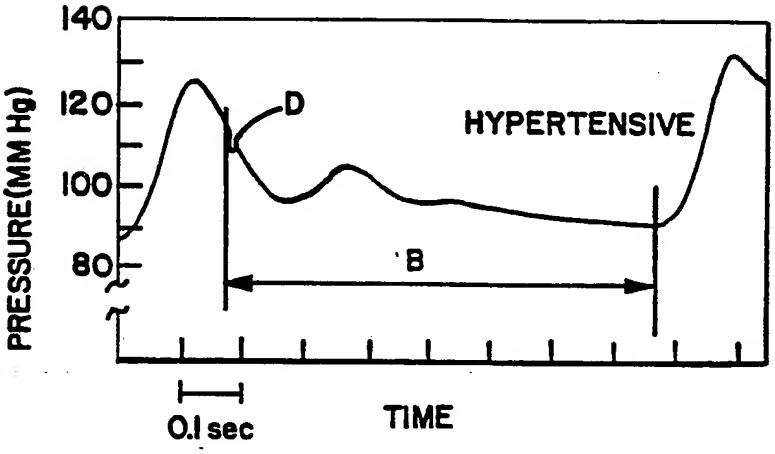

140
120
100
80
PRESSURE (MM Hg)
D
HYPERTENSIVE
B
0.1 sec
TIME

FIG. 8

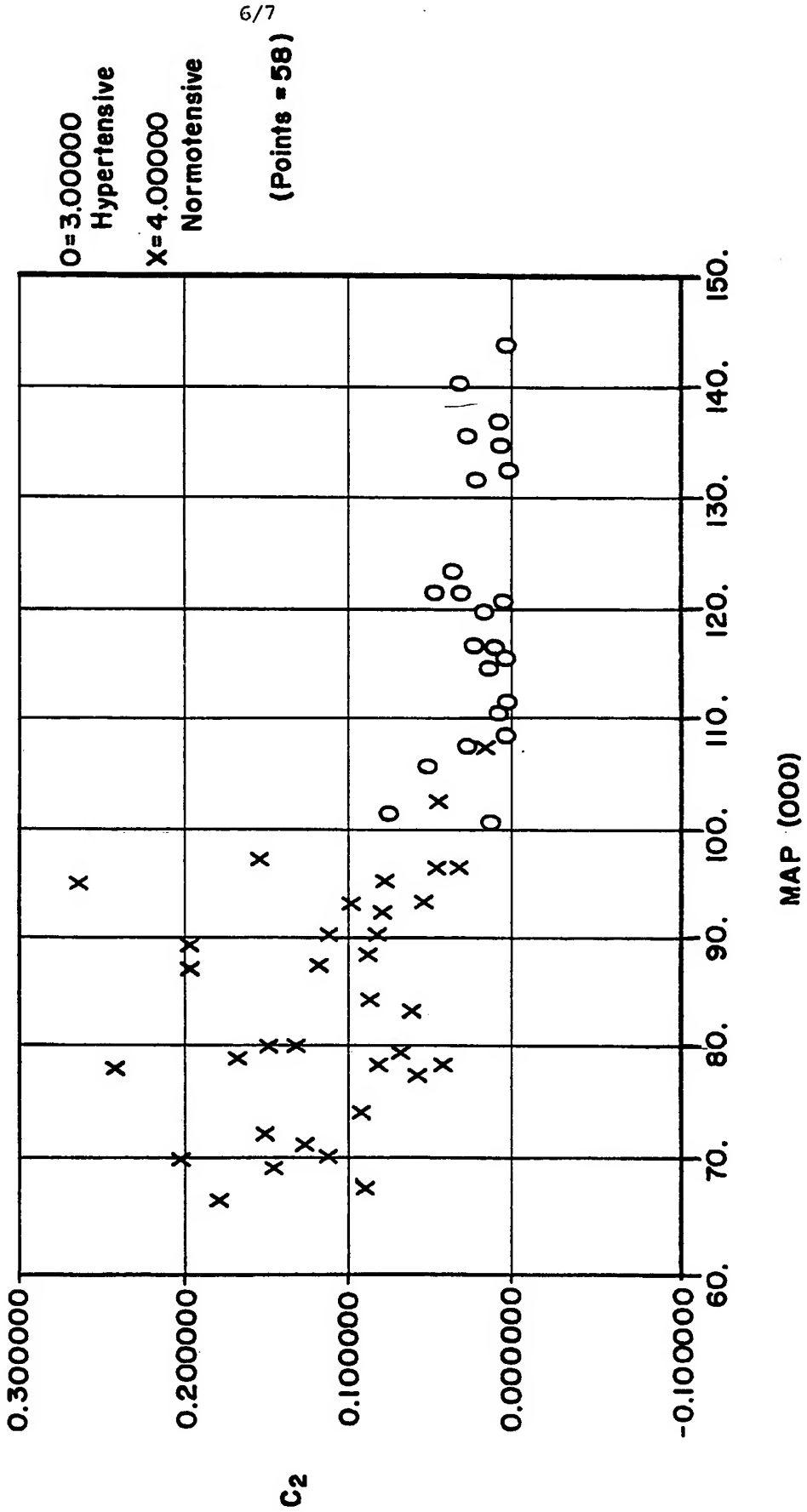
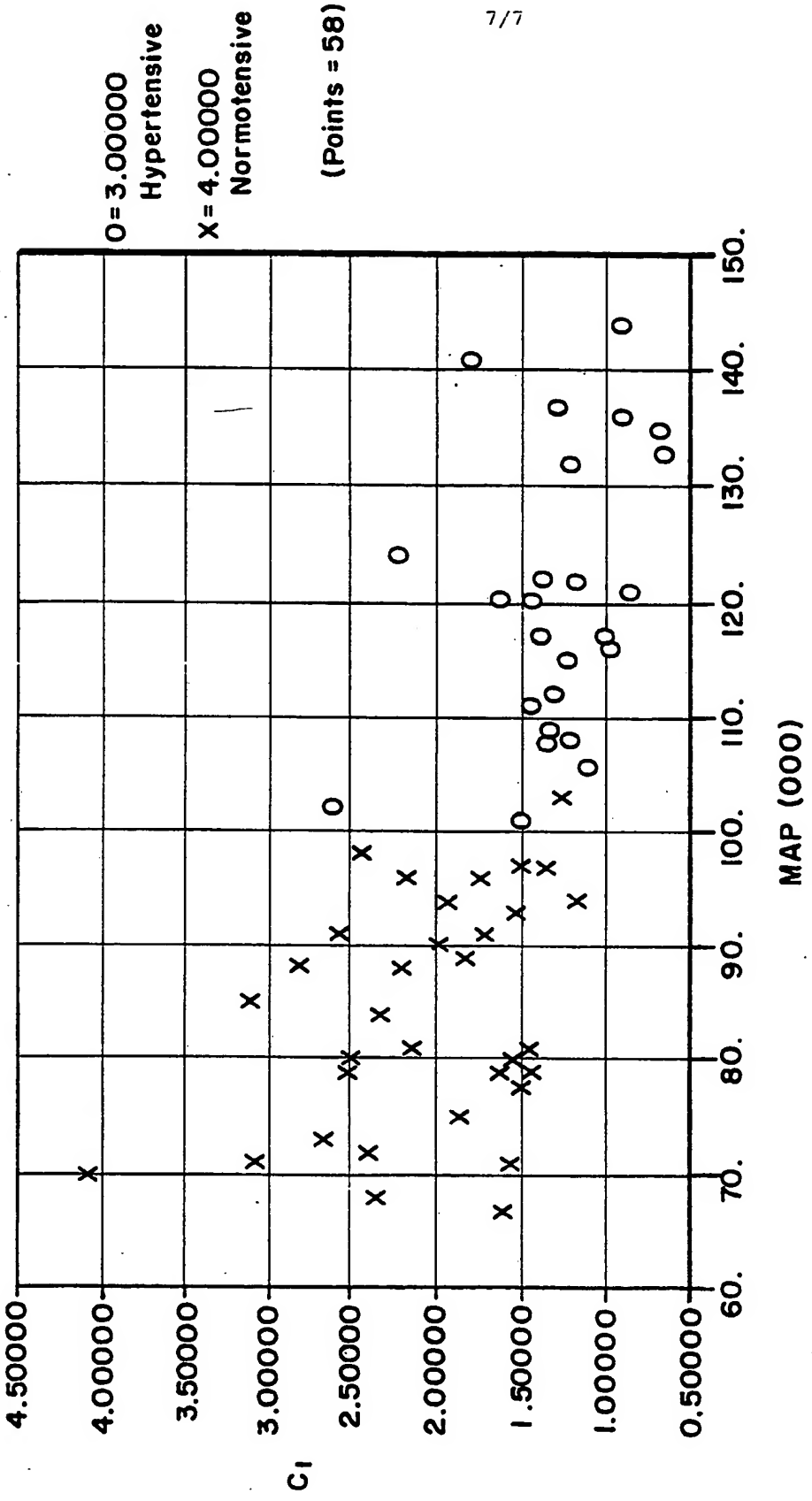

O=3.00000 Hypertensive
X=4.00000 Normotensive
(Points = 58)
0.300000
0.200000
0.100000
0.000000
-0.100000
C_2
60.
70.
80.
90.
100.
110.
120.
130.
140.
150.
MAP (000)

FIG. 9


O= 3.00000 Hypertensive
X= 4.00000 Normotensive
(Points = 58)
4.50000
4.00000
3.50000
3.00000
2.50000
2.00000
1.50000
1.00000
0.50000
C1
60.
70.
80.
90.
100.
110.
120.
130.
140.
150.
MAP (000)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/03613

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [8]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 B 5/021

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Journal of Applied Physiology, vol. 40, no. 2, February 1976 The American Physiological Society Rockville Pike (US) T.B. Watt et al.: "Arterial pressure contour analysis for estimating human vascular properties", pages 171-176, see the whole document esp. table 2 (cited in the application) --	1,3-7
A	IEEE Transactions on Bio-Medical Engineering vol. BME-14, no. 1, January 1967 IEEE (New York, US) R.M. Goldwyn et al.: "Arterial pressure pulse contour analysis via a mathematical model for the clinical quantification of human vascular properties", pages 11-17, see the whole document esp. table II (cited in the application) --	1,3-7

./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13th November 1989	15. 12. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	T.K. WILLIS

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Medical & Biological Engineering, vol. 9, no. 5, September 1971 Pergamon Press, (Stevenage, GB) H.-G. Karlsson et al.: "Numerical analysis of pressure and flow pulsations in a segment of the arterial tree", pages 431-445 see the whole document --	1,7
A	Medical & Biological Engineering & Computing, vol. 15, 1977 Pergamon Press, (Stevenage, GB) G. Warner et al.: "Circulation model for monitoring arterial systolic blood pressure", pages 81-89 see the whole document --	1,7
A	GB, A, 1538695 (BIOTRON MEDICAL PRODUCTS, LTD) 24 January 1979, see appendix A; pages 6-14	1,7

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND incompletely searchable

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-12, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8903613 SA 30875

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/12/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1538695	24-01-79	None	